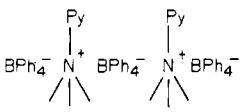
spective monomer to excimer ratios are approximately 0.13, 0.33, 0.55, and 0.9 for P18C6/$PN^+$ = 1.0, 3.0, 7.5, and 30 (all complex is polymer bound when P18C6/$PN^+$ > 2.5). Even at high P18C6/$PN^+$ ratios, when the excimer emission of bound $PN^+$ disappears, the binding of $PN^+$ is still strongly enhanced by the presence of $BPh_4^-$. In that case, the bound $PN^+$ may be in the form of an ion pair $PN^+BPh_4^-$ which is expected to have a higher binding constant to P18C6 than the free $PN^+$ ion.

It may be argued that the strong binding of $(PN^+)_2(BPh_4^-)_3$ to P18C6 is caused by $Na^+$ binding to P18C6. This would convert P18C6 into a polycation which then interacts electrostatically with the negatively charged complex. However, the binding constant of $Na^+$ to P18C6 in water is only 2.4 $M^{-1}$,[12] and under our conditions ([$NaBPh_4$] < $5 \times 10^{-5}$ M) binding of $Na^+$ to P18C6 would be negligibly small. On the other hand, $Na^+$ binding to P18C6 may be enhanced as a result of the strong binding of the anionic complex to P18C6, which especially under saturation conditions converts P18C6 into a polyanion of rather high charge density.

The large number of $PN^+$ molecules that can be adsorbed onto P18C6 in the presence of $BPh_4^-$ suggests that under these conditions the pyrene molecules and, thus, the complexes are now located close to the periphery of the coiled P18C6 chain. It could be speculated that the ability to accommodate so many $PN^+$ molecules is accomplished by insertion of the planar pyrene ring in between adjacent benzocrown ether ligands with the trimethylammonium cationic ends protruding into the aqueous phase and paired to $BPh_4^-$ ions. The stability of the $(PN^+)_2(BPh_4^-)_3$ aggregate (or a multiple of this complex) in water may in part derive from ground-state interactions between the two pyrene moieties as suggested in the drawing below, causing the optical absorption of pyrene to shift from 342 to 352 nm and the monomer emission spectrum to change to an excimer spectrum. Apparently, this structure is maintained to some degree when the complex binds to P18C6, at least when the ratio P18C6/$PN^+$ is not too large. More information on the location of P18C6-bound $PN^+$ in the presence and absence of $BPh_4^-$ could probably be obtained by addition of pyrene quenchers, and such studies are being planned.




Preliminary studies have revealed that $PN^+$ binding to P18C6 is also enhanced by anions like $SCN^-$ or $I^-$ even when added in the form of their potassium or cesium salts. These cations bind to P18C6, and their presence should actually decrease $PN^+$ binding to P18C6 as was also demonstrated in the binding of the cationic fluorophor auramine 0.[9] In comparison to $BPh_4^-$, much higher concentrations ($\approx 10^{-2}$ M) of $SCN^-$ or $I^-$ are needed to enhance $PN^+$ binding to P18C6, and it is possible that under these conditions ion pairing with $PN^+$ occurs which in turn causes the increased binding to P18C6.

In conclusion, our studies demonstrate that even at very low concentrations hydrophobic ions of opposite charge aggregate into complexes of well-defined stoichiometry (in our system 2:3) which then cluster into higher aggregates under formation of a coacervate phase. The aggregation profoundly affects the binding of these solutes to neutral polysoap-type molecules like poly(vinylbenzo-18-crown-6), and probably also to micelles or to macromolecules with hydrophobic regions such as proteins. It especially increases the total number of solute molecules that can be bound to the poly(crown ether). The aggregation also causes changes in the optical and fluorescence spectra of the solutes e.g., the formation of excimers. Since these solutes are frequently used to probe the structures of micelles and biological macromolecules, the observed phenomena may have important implications in these fields of study.

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**Registry No.** $PN^+$, 81341-11-9; $BPh_4^-$, 4358-26-3; Pl8C6, 31943-71-2.

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# Electrochemical Behavior of a Dopamine Polymer. Dopamine Release as a Primitive Analogue of a Synapse

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**Abstract:** A modified polystyrene was synthesized and characterized which held *N*-(2-(3,4-dihydroxyphenyl)ethyl)isonicotinamide units. This polymer was dissolved in DMF, syringed onto glassy carbon electrodes, and dried; the electrode was then used in aqueous electrolyte solutions. In pH 7 solution, at potentials more negative than −0.9 V (SCE), cathodic current caused cleavage of the amide linkage and release of the neurotransmitter dopamine. The released dopamine was detected at a second electrode by its oxidation or by HPLC. Voltammetric studies of the reduction process as well as the oxidation of the hydroquinone units in the polymer layer were performed. It was shown that only a few equivalent monolayers of polymer units could be oxidized or reduced even if the layer contained many more such units. The oxidation of solution-phase NADH on these electrodes was studied voltammetrically. It was shown that the polymer acted as an electrocatalyst. Quinone units were formed on the polymer and they in turn oxidized NADH molecules. Maximum catalytic efficiency was obtained with a layer holding approximately one equivalent monolayer of dopamine units.

The conduction of electrical signals in vivo involves chemical communication between neutrons.[1] At a synapse, transmitter substances are released from the presynaptic terminal in response to a change in the neuron's potential. These neurotransmitters diffuse across a small volume of solution, the synaptic cleft, and then are detected at receptor sites on the postsynaptic membrane. We have recently reported that a solid electrode, modified with a thin layer of a suitable polymer, will similarly respond to a change in potential to release the neurotransmitter, dopamine.[2]

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0002-7863/83/1505-5271$01.50/0 

The released dopamine can be detected at a nearby second electrode. In this way a primitive analogue of a synapse can be constructed. This paper includes a complete description of that work.

The electrode described here is a prototype for a device which could be used to deliver small amounts of biomedically interesting materials to specific locations at specific times. As described in the accompanying paper,[3] such a device could have utility to neuroscientists interested in the action of drugs and neurotransmitters at the single neuron level.

Although our focus has been neurotransmitter delivery, the basic concept of releasing chemicals from a surface at an appropriate moment in response to an electrical signal has a more general, intrinsic importance. In addition, the study of this phenomenon should allow further insight into the nature of chemically modified electrodes. Of the several ways that molecules can be attached to electrode surfaces, modification with polymers is clearly the approach of choice, since it will allow the possibility for delivering more material than methods giving monolayers of modifier. Polymeric films can be developed on a surface by a variety of methods.[4] We have chosen to coat a prebuilt polymer onto an electrode from a solvent in which the polymer is soluble.[5] After drying, the coated electrode is used in aqueous electrolyte. In this medium the polymer is insoluble and it adheres to the surface. This method has the advantage that the structure and the amount of polymer are well known when the electrochemical experiment is initiated. Methods in which monomeric material is polymerized onto the electrode can give films which adhere more strongly, but the exact composition and the amount of polymer on the electrode are difficult to determine and usually unknown.

In this paper we discuss not only the release and detection of dopamine, but also the use of this polymer electrode, as a catalyst for the oxidation of NADH in solution, and we emphasize in each of these studies the fundamental problem of charge propagation through electroactive polymer films on electrodes. This is a problem of considerable current interest.[4] It has been recognized that four mechanistic components must be considered in describing this process. The first is the heterogeneous redox process at the interface between the polymer layer and the underlying conductor. Following this are three cooperating or competing changes by which charge can be propagated through the film. They are ionic diffusion through the film, polymer chain motion, and redox exchange reactions between units in the film. Most studies have utilized electroactive groups in the film which only undergo one-electron transfer reactions. With these units the propagation of redox reactions through the layer can be relatively rapid and it has often been proposed that electrons "hop" from one unit to the next. This must involve cooperative polymer motion and ionic diffusion to balance the charge and accommodate the necessary structural changes. In the present study it was found that such a hopping mechanism was not effective.

## Experimental Section

**Chemicals.** Chloromethylated styrene (40% para, 60% meta) was obtained from Polysciences. β-NADH was obtained from Sigma Chemical Co. Potassium chloride and pH buffer solutions were obtained from Fisher Scientific Co. Other chemicals were obtained from Aldrich Chemical Co. and were used without further purification.

**Electrochemical Measurements.** Electrochemical experiments were performed with a Princeton Applied Research (PAR) 173 potentiostat in conjunction with a PAR 175 universal programmer. Voltammograms were recorded on a Houston Instrument Omnigraphic 2000 X-Y recorder. Working electrodes were glassy carbon rods obtained from Normar Industries. In the case of cyclic voltammetry, a glassy carbon disk, $^1/_8$ in. in diameter and $^1/_2$ in. in length, was cut from a rod and sealed in heat-shrinkable Teflon tubing with an exposed area of $7.93 \times 10^{-2}$ cm$^2$. Glassy carbon electrodes, $^1/_4$ in. in diameter and 2 in length, sealed at one end into a glass tubing with S-208 epoxy (obtained from Devcon Corp., Danvers, MA) were used for preparative electrolysis. All carbon electrodes were cleaned and polished by abrasion with Magomet Polishing Compound No. 40-6440AB (obtained from Buehler Ltd., Evanston, IL) on polishing cloth, rinsed thoroughly with a jet of distilled water, and air-dried. All potential measurements were referred to a saturated calomel electrode (SCE). Test solutions were pH buffer solutions containg 0.1 M potassium chloride as supporting electrolyte, unless otherwise specified, and were prepared just prior to each experiment and degassed by bubbling with water-saturated argon at least half an hour. Coatings of the polymers were prepared by syringing aliquots of polymer solutions in DMF onto a glassy carbon disk electrode and allowing the solvent to evaporate slowly. (Rapid evaporation gave rough and uneven polymer coatings as revealed under a microscope.) Electrodes prepared by the above procedure were used within half an hour.

**Chromatographic Analyses.** Gas chromatography (GC) was performed with a Varian 3700 in conjunction with a Perkin-Elmer M-2 calculating integrator. The column was a deactivated glass column packed with Chromosorb 7500 coated with 6% Carbowax-20M and 1.5% KOH. Helium was used as the carrier gas.

High-pressure liquid chromatography (HPLC) was performed with a Waters Associates System: Solvent Delivery System 6000A, Solvent Programmer 660, and Absorbance Detector 400 set at 254 mμ. It was in conjunction with a Perkin-Elmer M-2 calculating integrator. An ultrasphere ODS column, 5 μm, 4.6 mm × 15 cm, was used with 0.05 M phosphate buffer, pH 2.3, as solvent. The solvent was very well degassed with argon before use.

***N*-(*n*-Butyl)isonicotinamide (2).** A solution of 1.20 g (9.75 mmol) of isonicotinic acid in 20 mL of thionyl chloride was refluxed gently for 4 h. Any excess of $SOCl_2$ was removed under reduced pressure. To this residue, 50 mL of dry chloroform was added with stirring. The mixture was chilled in an ice bath and 2.5 mL (17.94 mmol) of triethylamine and 1.5 mL (15.20 mmol) of *n*-butylamine were added. The resulting solution was stirred at room temperature for an additional 8 h. At the end of the reaction, the chloroform solution was washed with two 50-mL portions of saturated sodium bicarbonate solution and three 50-mL portions of water, dried with anhydrous $MgSO_4$, and decolorized with charcoal. The solvent was removed under reduced pressure and the residue recrystallized from ether–pentane to give 1.386 g (77%) of *N*-(*n*-butyl)isonicotinamide (**2**), mp 62–64 °C (lit.[6] 63–75 °C): IR (KBr) 3300, 3060 (w), 2980, 2940, 2880, 1640, 1600 (w), 1550, 1310, 850, 760 cm$^{-1}$; NMR ($CDCl_3$) δ 0.95 (t, 3 H), 1.02–1.77 (m, 4 H), 3.46 (q, 2 H), 6.53 (t, 1 H), 7.46 (dd, 2 H), 8.71 (dd, 2 H). Anal. Calcd for $C_{10}H_{14}N_2O$: C, 67.29; H, 7.92; N, 15.72; O, 8.98. Found: C, 67.37; H, 7.70; N, 15.52; O, 9.06.

**1-Benzyl-4-(*n*-butylcarbamoyl)pyridinium Chloride (3).** To a solution of 0.857 g (4.81 mmol) of **2** in 30 mL of dry toluene, 7.0 mL (6.08 mmol) of benzyl chloride was added. The resulting solution was stirred at room temperature for 8 h. The precipitate was filtered and recrystallized from ethyl alcohol–ethyl acetate to give 1.27 g (91%) of **3**, mp 173–174 °C: IR (KBr) 3200, 3050, 3010, 2980, 2950, 2890, 1660, 1564, 1550, 1510, 1465, 1450, 1300, 1135, 870, 750, 700 cm$^{-1}$; NMR ($CDCl_3$) δ 0.90 (t, 3 H), 1.05–1.81 (m, 4 H), 3.48 (q, 2 H), 6.31 (s, 2 H), 7.28–754 (m, 5 H), 9.03 (d, 2 H), 9.51 (d, 2 H), 10.14 (t, 1 H). Anal. Calcd for $C_{17}H_{21}N_2OCl$: C, 66.99; H, 6.94; N, 9.19; O, 5.25. Found: C, 66.77; H, 7.01; N, 9.19; O, 5.35.

**Poly(chloromethylated styrene) (4).** A solution of 5 mL of chloromethylated styrene in 75 mL of toluene was washed with three 10-mL portions of 5% sodium hydroxide solution, two 10-mL portions of water and dried with anhydrous $MgSO_4$. The resulting solution was degassed with dry nitrogen and a catalytic amount (0.1 g) of benzoyl peroxide was added. After 3 h of refluxing, the solvent was removed under reduced pressure and the residue was redissolved in 4 mL of chloroform. To the chloroform solution, methanol was added dropwise with vigorous stirring until a milky suspension was obtained. This suspension was in turn added to 200 mL of stirring methanol. The precipitate was filtered, washed with plenty of methanol, and air-dried. The precipitate was then dissolved in 4 mL of chloroform. The precipitation of the polymer was repeated using methanol and the final white precipitate was washed with 5% sodium bicarbonate solution, water, and methanol and air-dried to yield 1.84 g

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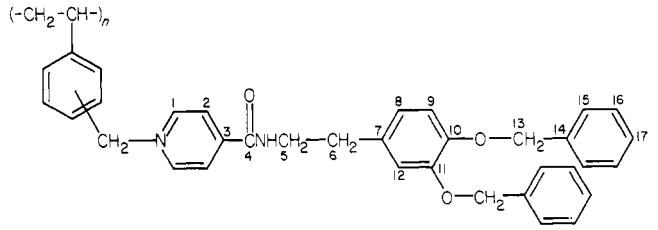
Table I. $^{13}C$ NMR Data ($Me_2SO$-$d_6$)



| atom | 5 | 6 | 1 |
|---|---|---|---|
| 1 | 151.89 | 145.71 | 148.44 |
| 2 | 122.92 | 127.29 | 125.87 |
| 3 | 143.54 | 137.13 | 145.26 |
| 4 | 166.56 | 161.31 | 161.31 |
| 5 | 42.78 | 41.94 | 41.64 |
| 6 | 36.24 | 33.98 | 33.99 |
| 7 | 129.17 | 127.39 | 129.56 |
| 8 | 123.28 | 121.08 | 119.02 |
| 9 | 117.79 | 115.03 | 115.86 |
| 10 | 150.51 | 148.17 | 144.97 |
| 11 | 149.03 | 146.66 | 143.50 |
| 12 | 117.28 | 114.63 | 115.05 |
| 13 | 72.61 | 70.15 | |
| 14 | 139.62 | 123.20 | |
| 15 | 134.62 | 132.10 | |
| 16 | 130.00 | 128.14 | |
| 17 | 129.34 | 127.52 | |

of **4**. The polymer softened at 125 °C and melted at 140 °C: IR (KBr) 3050, 3020, 2920, 2840, 1605, 1585, 1510, 1485, 1440, 1420, 1265, 790, 750 $cm^{-1}$. Anal. Calcd for $C_9H_9Cl$: C, 70.83; H, 5.94; Cl, 23.23. Found: C, 70.66; H, 6.07; Cl, 23.43.

***N*-Isonicotinoyl-3,4-(dibenzyloxy)phenethylamine (5).** A solution of 1.14 g (9.3 mmol) of isonicotinic acid in 15 mL of thionyl chloride was refluxed for 8 h. Any excess of thionyl chloride was removed by distillation under reduced pressure. To the residue, 50 mL of dry dioxan and 3.53 g (9.6 mmol) of 3,4-(dibenzyloxy)phenethylamine hydrochloride was added. The mixture was cooled in an ice bath and 7 mL of triethylamine was added dropwise over a period of 20 min with constant stirring. The mixture was stirred at room temperature for an additional 10 h. The solvent was removed under reduced pressure and 120 mL of chloroform was added. The mixture was washed with three 50-mL portions of water, dried with anhydrous $MgSO_4$, and decolorized with charcoal. The chloroform was removed again under reduced pressure and the residue was dissolved in 20 mL of boiling ethyl ether. The ethereal solution was stored in a refrigerator overnight for recrystallization. The crystals were filtered, washed with *n*-hexane, and air-dried to yield 2.93 g (72%) of **5**, mp 130–132 °C: IR (KBr) 3360, 3300, 3060, 3030, 2940, 2860, 1645, 1600, 1545, 1520, 1310, 1260, 1230, 1140, 1025, 845, 805, 750 $cm^{-1}$; NMR ($Me_2SO$-$d_6$) $\delta$ 2.79 (t, 2 H), 3.56 (q, 2 H), 5.09 (s, 4 H), 6.69 (m, 3 H), 7.39 (m, 10 H), 7.75 (dd, 2 H), 8.73 (dd, 2 H). $^{13}C$ NMR data are listed in Table I. Anal. Calcd for $C_{28}H_{26}N_2O_3$: C, 76.69; H, 5.98; N, 6.39; O, 10.95. Found: C. 76.47; H, 6.01; N, 6.07; O, 11.17.

**Preparation of Polymer 6.** A solution of 1.0 g (2.3 mmol) of **5** and 0.34 g (2.2 mmol) of **4** in 20 mL of dry toluene was heated at 80–85 °C with constant stirring over a period of 3 days. The waxy product was occasionally loosened from the wall of the reaction vessel by means of a spatula. At the end of the reaction, the mixture was cooled to room temperature and the precipitate was filtered, washed with hot toluene (50–60 °C), and dried to give 1.19 g (85%) of **6** which softened at 160 °C: IR (KBr) 3400, 3200, 3020, 2920, 2850, 1665, 1555, 1510, 1450, 1425, 1380, 1305, 1260, 1220, 1135, 1020, 740, 695 $cm^{-1}$. $^{13}C$ NMR data are listed in Table I. Anal. Calcd for $C_{37}H_{35}N_2O_3Cl \cdot H_2O$: C, 72.95; H, 6.12; N, 4.60; O, 10.50; Cl, 5.80. Found: C, 73.01; H, 6.33; N, 4.35; O, 10.37; Cl, 5.90. The loading was calculated to be 1.55 mmol/g (95% loading).

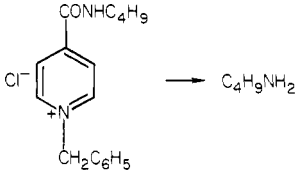
**Preparation of Polymer 1.** A solution of 1.19 g (2.0 mmol) of **6** and 12 mL (91.3 mmol) of thioanisole in 30 mL of trifluoroacetic acid was stirred at room temperature over a period of 30 h. The volume of the solution was reduced to ~10 mL under reduced pressure at ~40 °C. With vigorous stirring, 100 mL of toluene was added into the condensed solution. The supernatant solution was decanted and the residue was dissolved in 10 mL of hot DMF. To 200 mL of dry toluene the DMF solution was added in a fine stream with constant stirring. The precipitate was filtered, washed with plenty of toluene and air-dried to give 0.42 g of **1** which softened at 158 °C: IR (KBr) 3250 (b), 3060, 2930, 1665 (s), 1600 (w), 1560, 1540, 1510, 1445, 1290, 1200 (s), 1130, 870, 830, 800, 720 $cm^{-1}$. $^{13}C$ NMR data are listed in Table I. Anal. Calcd for $C_{25}H_{23}N_2O_5F_3$: C, 61.47; H, 4.75; N, 5.73; F, 11.67. Found: C, 61.35; H, 4.93; N, 5.50; F, 11.49.

**Electrochemical Reduction of 1-Benzyl-*N*-(*n*-butyl)isonicotinamide.** The electrolysis of **3** was carried out in a divided cell at −1.0 V (SCE). A glassy carbon rod, $^1/_4$ in. in diameter 2 in. in length, was used as a cathode and graphite rods were used as anodes. The catholyte (7 mL) contained 0.49 mmol of **3** and was 0.5 N in NaCl and 0.05 M in pH 7 phosphate buffer, whereas the anolyte was 35 mL of pH 7 phosphate buffer containing 0.5 N NaCl. The electrolyte was degassed by bubbling argon for at least 20 min before electrolysis. The reduction was terminated after 120 C of charge had been passed. Gas-chromatographic analysis of the catholyte gave positive result for the presence of *n*-butylamine.

## Results and Discussion

**A. The Polymer.** A central concept here is that a polymer can be prepared in which molecules of the active compound, i.e., dopamine, are held to the polymer backbone by cathodically cleavable bonds. Our attention focused on the release of amines. The literature abounds with reductive reactions which "deprotect" or release amines, but surprisingly, the electrochemical examples are almost exclusively done using nonaqueous media. Because we had in vivo experiments in mind, we wished to use only aqueous electrolytes. An amide cleavage of isonicotinamides in DMF reported by Lund[7] seemed to offer a lead, and this work follows that lead.

Preliminary experiments were performed using amide **3**. Cyclic voltammetry demonstrated that this compound would reduce in aqueous pH 7 media; $E_p$ = −0.87 V (SCE) at a sweep rate, $\nu$ = 0.1 V $s^{-1}$. A preparative electrolysis followed by gas chromatographic analysis showed that reduction at −1.0 V in aqueous 0.5 N NaCl solution did produce butylamine.



**3**

With this experiment as encouragement, polymer **1** was prepared according to Scheme I. This polymer had three components: the polystyrene, which made it strongly adhere to the electrode; the cationic isonicotinate, which served as a good electron acceptor; and the neurotransmitter, dopamine. Compound **5** and the polymer **6** were fully characterized by NMR, IR, and elemental analysis. Polymer **1** was isolated as the trifluoroacetate salt and was similarly analyzed. The apparent loading, calculated from the elemental analysis, varied somewhat from preparation to preparation. The material used for the experiments reported here was loaded to the extent of 96%. The most useful structural technique was $^{13}C$ NMR. Since the isonicotinate and dopamine carbon atoms gave sharp lines and model compounds were available, it was possible to assign all of the $^{13}C$ NMR lines (Table I), and in this way to assure purity and structure. A particular problem in the synthesis was removal of the benzyl protecting groups. The $^{13}C$ NMR spectrum clearly revealed this problem and indicated that of several methods tried the "push–pull" hydrolysis system of trifluoroacetic acid in thioanisole[8] was the only fully effective one.

**B. Electrically Stimulated Release of Dopamine.** The main goal of this study was to demonstrate that an electrode coated with polymer **1** (called electrode I) would respond to a cathodic current pulse and release dopamine into solution. Therefore, although voltammetric studies chronologically preceded the product studies, the former are described later. Glassy carbon electrodes were selected for use because they are inert over a large potential range in aqueous solution. Specifically, at pH 7 there is a small

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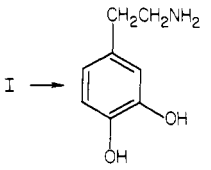
(8) Kiso, Y.; Ukawa, K.; Nakamura, S.; Ito, K.; Akita, T. *Chem. Pharm. Bull.* **1980**, *28*, 673.



background current out to about −1.3 V (SCE). Modified electrodes were prepared by dip-coating or by syringing 0.5–10 μL aliquots of a solution of **1** in DMF onto the horizontal surface of a cleaned glassy carbon disk. Slow evaporation of the solvent at room temperature gave coated electrodes I.

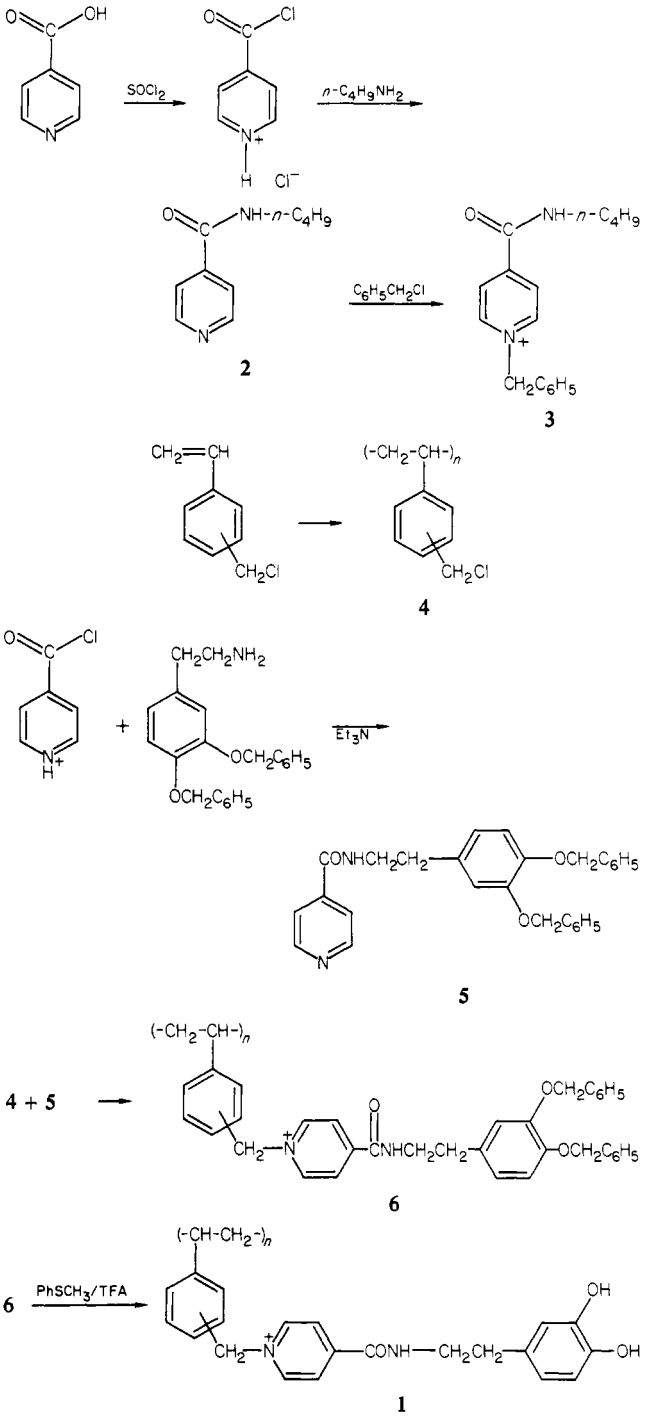
Voltammetry demonstrated that electrodes I gave cathodic reduction peaks near −0.9 V and a quasireversible couple due to the hydroquinone moiety of **1** near +0.2 V. The currents were quite small ($Q$, the integrated charge, varied from $10^{-10}$ to $10^{-8}$ F cm$^{-2}$) and it was clear that detection of any released dopamine would be difficult. Two types of experiments have been performed. One was previously described[2] in which a set of 40 electrodes was prepared by dip-coating glassy carbon rods from a solution of **1** in DMF. Individually, these electrodes were taken to −1.2 V so that dopamine might be discharged into a single 10-mL volume of degassed, buffered electrolyte solution. After completion of the 40 electrolyses, the catholyte was analyzed by using high-pressure liquid chromatography (HPLC). Dopamine was present. A control experiment consisted of soaking 40 coated electrodes in 10 mL of electrolyte for an equivalent time with no electrolysis. No dopamine could be detected in the solution.

This experiment made it clear that dopamine was released in response to the cathodic current pulse. However, the experiment was awkward and it was not possible to get accurate quantitative yield data. Since the released dopamine could be detected electrochemically, it was realized that a better experiment involved the use of a thin layer electrochemical cell.[9] Since we wished to use a glassy carbon electrode and it was necessary to do many experiments with cleaning and polymer coating between each one, an unelaborate cell was devised. As previously described,[2b] a droplet of aqueous electrolyte was held between two horizontal carbon disks. One of these was electrode I ($\Gamma = 3.0 \times 10^{-9}$ mol cm$^{-2}$ of dopamine units) and the other a bare carbon electrode.

We have pointed out that this cell is a primitive analogue of a synapse.[2b] Electrode I corresponds to the presynaptic terminal, where dopamine is released in response to an electrical signal; the droplet, typically 5 μL, corresponds to the cleft. Released dopamine was to be detected at the second, "postsynaptic", electrode.

The experiment was conducted by assembling the cell, cycling the potential of a presoaked electrode I from 0.0 to −1.2 V, and then cycling the potential of the postsynaptic electrode from 0.0 to +0.4 V. The solvent was 0.1 M KCl containing 0.05 M buffer and both the anodic and cathodic sweep rates were 0.1 V s$^{-1}$. At pH 7, dopamine was detected by the characteristic anodic peak at 0.18 V, $i_p$ = 125 nA, and on the return half-cycle by the cathodic peak at 0.10 V, $i_p$ = 75 nA. This identification was double-checked using HPLC on the droplet. In control experiments no dopamine was detected when electrodes were presoaked as described[2b] and no current was passed. When the presoak was eliminated, small electrochemical signals due to some hydroquinone were observed even without electrolysis. This is probably due to polymer desorption. The amount of dopamine released was quantitated under a variety of conditions. A quantitation curve was generated using standard 5 μL solutions of dopamine in aqueous buffer and measuring the anodic peak current in linear sweep voltammetry on the postsynaptic electrode. In an experiment like the one described above, where the surface concentration of dopamine units $\Gamma = 3 \times 10^{-9}$ mol cm$^{-2}$ and pH = 7, the dopamine yield was only 5%. In separate experiments, the pH was varied. As shown in Table II, the yield increased to 20% at pH 2. Even at low pH, the amounts released are very small. It was our initial hope that larger amounts of **1** on the electrode would deliver larger amounts into the solution. This did not prove to be correct, as shown by the last entries of Table II. Note that these yields are based on the amount of **1** added to the surface. This inefficiency corresponds to our observation that thicker layers of polymer **1** do not give substantially larger cathodic currents.

Scheme I



**C. Cyclic Voltammetry of Electrodes I. 1. Overview.** Electrodes I were prepared by syringing on a known amount of polymer **1**. This method gave peak potentials, $E_p$, reproducible to ± 5 mV and $i_p$ good to ±15%. An electrode with an initial surface concentration $\Gamma_i = 3.34 \times 10^{-8}$ mol cm$^{-2}$ was studied using 0.1 M KCl and 0.05 M, pH 7 phosphate buffer. Sweeping at 0.1 V s$^{-1}$ from 0.0 to −1.2 V (SCE) gave a reduction peak with $E_p$ = 0.88 V (Figure 1). On the return half-cycle a small very broad anodic peak was present. On the second and succeeding sweeps there were successively smaller cathodic peaks until the background trace was reached after about ten cycles. An identically prepared

(9) Anderson, L. B.; Reilley, C. N. *J. Electroanal. Chem.* **1965**, *10*, 295, 538.

**Table II.** Yields of Dopamine Released from a Carbon Electrode Modified with Polymer **1**

| $\Gamma$ ($10^{-9}$ mol cm$^{-2}$)[a] | buffer, pH[b] | dopamine[c] (mol/L) × $10^6$ | yield (%) |
|---|---|---|---|
| 3 | phosphate, 7 | 2.4 | 5 |
| 3 | phosphate, 6 | 3.4 | 7 |
| 3 | phthalate, 4 | 6.7 | 14 |
| 3 | phthalate, 4 | 6.7 | 14 |
| 3 | phthalate, 3 | 8.2 | 17 |
| 3 | KCl/HCl, 2 | 9.6 | 20 |
| 0.7 | phosphate, 7 | 0.9 | 8 |
| 6 | phosphate, 7 | 1.0 | 1 |
| 9 | phosphate, 7 | 1.4 | 1 |

[a] Calculated from the amount syringed onto the surface. [b] Each electrolyte contained 0.1 M KCl and 0.05 M buffer. [c] Solution concentration of dopamine after release.

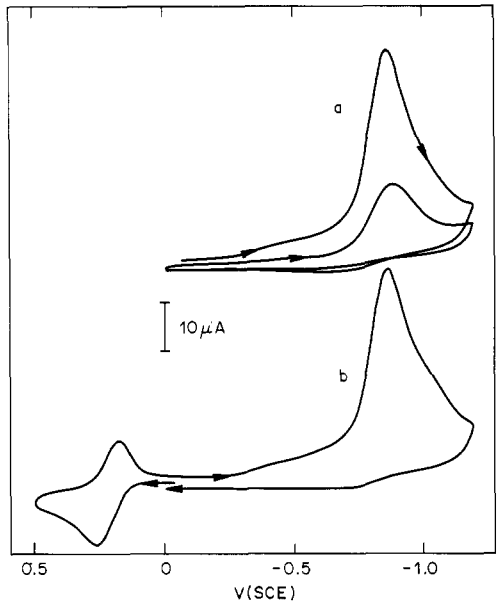



**Figure 1.** Cyclic voltammogram of electrode I, $\Gamma_i = 3.34 \times 10^{-8}$ mol cm$^{-2}$, in 0.05 M pH 7 buffer, 0.1 M KCl, $\nu = 0.1$ V s$^{-1}$: (a) sweeping from 0.0 to −1.2 V, two cycles; (b) sweeping from 0.0 to 0.4 and then to −1.2 V.

electrode was cycled from 0.0 to 0.4 V at 0.1 V s$^{-1}$. An oxidation peak at +0.26 V and the corresponding reduction peak at +0.17 V were observed. On the second sweep from 0.0 to 0.4 V these peaks were still present although somewhat diminished in size.

A voltammogram recorded on a third identical electrode I sweeping ten cycles from 0.0 to −1.2 V then to +0.4 V no longer showed the peak at +0.26 V. On the other hand, using a fresh I with a sweep sequence from 0.0 to 0.4 to −1.2 (Figure 1b) showed all three peaks (+0.24, +0.17, and −0.88 V), as expected.

The behavior is consistent with expectations from model monomeric compounds in solution. The cathodic peak corresponds to reduction of the isonicotinamide and leads, at least in part, to release of dopamine. At 0.1 V s$^{-1}$ cleavage is not fast and there is some chemical reversibility. This accounts for the anodic peak as well as the cathodic peak on the second sweep. If cleavage to produce electroinactive polymer products was rapid, neither an anodic peak nor a cathodic peak on the second sweep is expected. The quasireversible couple near +0.2 V is fully in accord with previous experience for dopamine/dopaquinone units attached to polymers on electrodes.

In the following two sections more detailed studies on both the cathodic and anodic reactions are described. In addition, the use of electrode I in NADH oxidations is mentioned.

**2. Reduction of Electrode I.** The above observations indicate that the cathodic process involves cleavage of the isonicotinamide units and release of dopamine. It seemed likely that this cleavage reaction involved protons and so the pH dependence over the range

**Table III.** Cyclic Voltammetry Data for Electrode I as pH Varied[a]

| pH | $-E_p$ (mV) | $\delta$ (mV)[b] |
|---|---|---|
| 1.2 | 737 | 80 |
| 2.2 | 772 | 75 |
| 3.2 | 816 | 83 |
| 4.4 | 859 | 77 |
| 5.3 | 901 | 99 |
| 6.3 | 855 | 145 |
| 7.2 | 858 | 135 |
| 8.2 | 858 | 138 |
| 8.5 | 861 | 140 |
| 9.2 | 890 | |
| 9.7 | 900 | |
| 11.1 | 950 | 300 |
| 12.0 | 970 | 280 |
| 13.0 | 1015 | 280 |

[a] $\Gamma_i = 9.0 \times 10^{-9}$ mol cm$^{-2}$, $\nu = 50$ mV s$^{-1}$, 0.1 M KCl present with 0.05 M buffer. [b] Peak width at half-height.

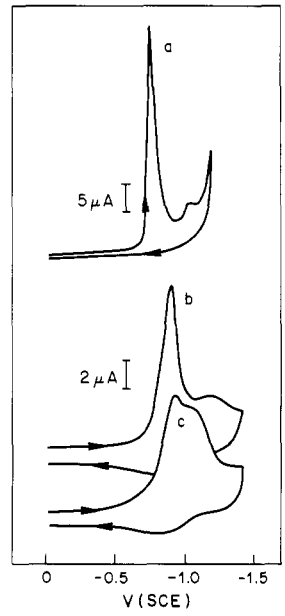



**Figure 2.** Cyclic voltammograms of electrode I, $\Gamma_i = 9.0 \times 10^{-9}$ mol cm$^{-2}$ in different buffer solutions, 0.1 M KCl, $\nu = 50$ mV s$^{-1}$: (a) pH 2.2 phthalate buffer, 0.05 M; (b) pH 8.5 phosphate buffer, 0.05 M; (c) pH 9.7 boric acid buffer, 0.1 M.

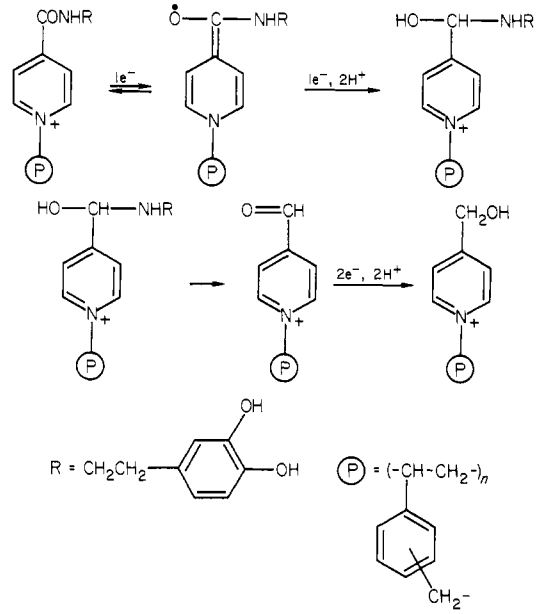
2–13 was investigated. The peak potentials $E_p$ and peak widths at half-height, $\delta$, are given in Table III. Sample voltammograms are found in Figure 2. In these experiments $\Gamma_i$ was $9 \times 10^{-9}$ mol cm$^{-2}$ and $\nu = 0.05$ V s$^{-1}$.

Below pH 6, the cathodic peak had a width of about 80 mV. There was no anodic peak on the return and no peaks on the second cycle. Thus, at low pH, in contrast to the behavior at pH 7 (or above), protonation reactions destroyed the originally electroactive groups during one sweep. In concert with this observation was a shift in $E_p$ to more negative values at higher pH. This shows that protons are involved in the rate-determining processes for reduction. Because the voltammogram shapes change, a plot of $E_p$ vs. pH is not readily interpreted.

Although far from definitive, all of the data quoted in this paper so far are consistent with the mechanism for cleavage shown in Scheme II.

Studies on model compounds indicated that cationic isonicotinaldehydes reduce as easily as cationic isonicotinamides. Therefore, it is possible that cleavage involves 4e$^-$, 4H$^+$ and generates the 4-pyridylmethanol. The structure of the polymer product which remains after cleavage is, however, not known. Scheme II also suggests that the anodic peak present at high pH and $\nu > 20$ mV s$^{-1}$ is due to oxidation of the one-electron reduction product. In nonaqueous solvents 1-alkyl-4-carboxamidopyridines are well known to reduce to relatively stable pyridinyl radical

Scheme II



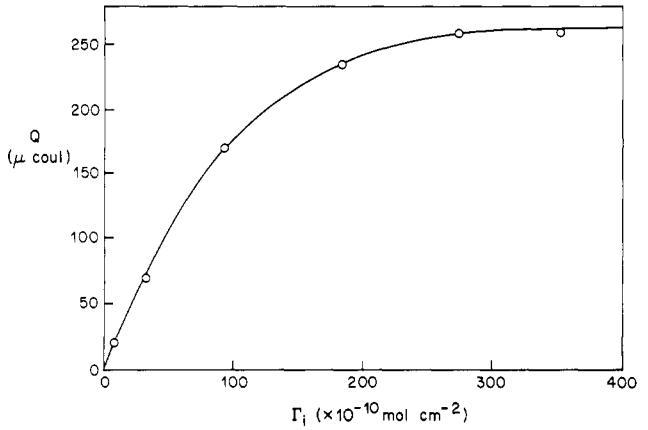




**Figure 3.** The dependence of cathodic charge, $Q$, on $\Gamma_i$, pH 7 phosphate buffer, 0.05 M, $\nu = 20$ mV s$^{-1}$.

products, and the electrochemistry of several isonicotinates has been characterized.[10] There are several alternative explanations and the unusual shape of the voltammogram precludes differentiating between them.

The charge passed during a single half-cycle from 0.0 to −1.2 V was estimated by integrating the background-corrected cyclic voltammograms for these $\Gamma_i = 9 \times 10^{-9}$ mol cm$^{-2}$ electrodes. Below pH 6, $Q$ was $8.6 \pm 0.4 \times 10^{-9}$ F cm$^{-2}$; between pH 6 and 8, $Q$ was $5.0 \pm 0.4 \times 10^{-9}$ F cm$^{-2}$. Since $Q$ is smaller than $\Gamma_i$ it is clear that only part of the layer is being reduced. Thus, it is proposed that charge propagates through the polymer layer only slowly. Figure 3 shows the dependence of $Q$ on $\Gamma_i$. At $\nu = 20$ mV s$^{-1}$ at pH 7 the total background corrected integral was measured for all sweeps until the trace returned to the background. The figure shows that at $\Gamma_i$ corresponding to about one equivalent monolayer, sufficient charge was passed to reduce 90% of the units added, if $n = 4$. As $\Gamma_i$ was increased, $Q$ increased to a limiting value of $3.4 \times 10^{-8}$ F cm$^{-2}$. This corresponds to about ten equivalent monolayers of isonicotinate units if $n = 4$. When $\nu = 0.1$ V s$^{-1}$ very similar results were obtained with $Q$ reaching a limiting value of about $3.7 \times 10^{-8}$ F cm$^{-2}$.

**3. The Hydroquinone/Quinone Couple.** Previous studies of the dopamine polymer **7** coated on glassy carbon showed that the

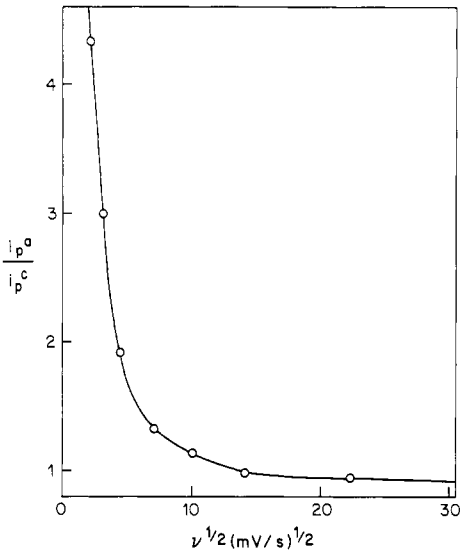



**Figure 4.** The stability of dopaquinone moiety as a function of scanning rate, $\nu$, in 0.05 M pH 7 phosphate buffer. $\Gamma_i = 8.25 \times 10^{-10}$ mol cm$^{-2}$.

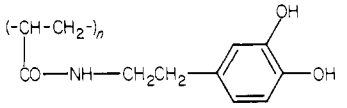
**Table IV.** Voltammetric Data for Electrode I at Positive $E^a$

| $\Gamma_i$ (mol cm$^{-2}$ × 10$^{-9}$) | $E_p^b$ (mV) | $i_p$ (μA) | $\Gamma_{coul}$ (mol cm$^{-2}$ × 10$^{-9}$) |
|---|---|---|---|
| 0.75 | 181 | 1.31 | 0.29 |
| 1.50 | 182 | 1.95 | 0.45 |
| 3.50 | 180 | 2.76 | 0.58 |
| 22.20 | 189 | 7.44 | 1.74 |
| 66.60 | 194 | 9.90 | 2.99 |
| 111.0 | 220 | 10.05 | 3.23 |

[a] pH 7 buffer, 0.1 M KCl, $\nu = 50$ mV s$^{-1}$. [b] Anodic peak.

dopamine units near the carbon surface were electroactive and bound dopaquinone was formed. The rate of interconversion was not very fast, so the couple is termed quasireversible. The dopaquinone was not entirely stable on the time scale provided by a sweep rate of 0.1 V s$^{-1}$. Similar observations have been reported for electrodes modified by absorption or covalent attachment of monomeric dopamine-type compounds[11] and electrodes modified by dopamine polymers.[12]

For polymer **7** on electrodes, it has also been demonstrated[12]




**7**

that only those dopamine units near the carbon surface are electroactive. Redox propagation through the layer is slow. This process can be speeded up by one-electron redox catalysts, e.g., a ferrocene, in the solution phase.[12]

Electrodes I behave in a very similar fashion to electrodes holding polymer **7**.

(a) Dopaquinone moieties are formed, but are unstable. As revealed by Figure 4 at slow $\nu$ there are virtually no dopaquinone units available for reduction on the return half-cycle and the ratio of cathodic and anodic currents, $i_p^c/i_p^a$, is small. At $\nu > 0.2$ V s$^{-1}$, the quinone units are stable and $i_p^c/i_p^a$ is about 1.0.

(b) Only the hydroquinone units near the carbon surface are electroactive. Table IV shows data taken at $\nu = 50$ mV s$^{-1}$ for various values of $\Gamma_i$. If $\Gamma_i$ is small, then $\Gamma_{coul}$ (calculated for $n = 2$) is equal to 40% $\Gamma_i$. As $\Gamma_i$ increases, $\Gamma_{coul}$ increases to a limiting value of about $3.5 \times 10^{-9}$ mol cm$^{-2}$. For "thick" layers

(10) Hermolin, J.; Levin, M.; Kosower, E. M. *J. Am. Chem. Soc.* **1981**, *103*, 4808. Nonaka, T.; Kato, T.; Fuchigami, T. and Sekine, T. *Electrochim. Acta* **1981**, *26*, 887. Kashti-Kaplan, S.; Hermolin, J.; Kirowa-Eisner, E. *J. Electrochem. Soc.* **1981**, *128*, 802.

(11) (a) Jaegfeldt, H.; Torstensson, A. B. C.; Gorton, L. G. O.; Johansson, G. *Anal. Chem.* **1981**, *53*, 1979. (b) Ueda, C.; Tse, D. C. S.; Kuwana, T. *Ibid.* **1982**, *54*, 850. (c) Tse, D. C. S.; Kuwana, T. *Ibid.* **1978**, *50*, 1315.

(12) (a) Degrand, C.; Miller, L. L. *J. Am. Chem. Soc.* **1980**, *102*, 5728. (b) Fukui, M.; Kitani, A.; Degrand, C.; Miller, L. L. *Ibid.* **1982**, *104*, 28.

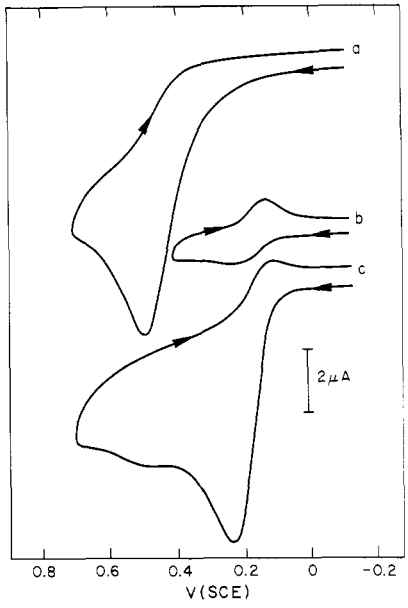



**Figure 5.** Catalytic oxidation of NADH on electrode I, $\nu = 50$ mV s$^{-1}$: (a) bare carbon disk in 0.5 mM NADH, pH 7 buffer, 0.1 M KCl; (b) electrode I, $\Gamma_i = 7.5 \times 10^{-10}$ mol cm$^{-2}$; (c) electrode I, $\Gamma_i = 7.5 \times 10^{-10}$ mol cm$^{-2}$ in solution a.

the redox propagation rate is not sufficient to allow oxidation of all the units. Regardless of $\Gamma_i$, the cathodic peak had $E_p = 110 \pm 5$ mV.

A set of three experiments were performed to see if this slow propagation rate could be accelerated by adding $K_4Fe(CN)_6$ to the solution. On a bare carbon disk, $1.1 \times 10^{-4}$ M $K_4Fe(CN)_6$ in pH 8 buffer, 0.1 M KCl gave $E_p^a = 250$ mV and $i_p^a = 1.3$ μA at $\nu = 50$ mV s$^{-1}$. Electrode I ($\Gamma_i = 3.0 \times 10^{-9}$ mol cm$^{-2}$) gave $i_p^a = 1.3$ μA in the absence of $K_4Fe(CN)_6$. If there were no interactions between $K_4Fe(CN)_6$ and the polymer, it was predicted that $i_p^a$ for $1.1 \times 10^{-4}$ on $K_4Fe(CN)_6$ on I would give $i_p^a \approx 2.6$ μA. For $\Gamma_i$ $3.0 \times 10^{-9}$ mol cm$^{-2}$ the $i_p^a$ of the merged peak is actually somewhat greater than the sum (3.0 μA). This increase may be due to the expected acceleration of the hydroquinone redox propagation, but it could also result from sequestering of the anion into the polymer layer. For $\Gamma_i = 5.4 \times 10^{-8}$ mol cm$^{-2}$ there is no current from $Fe(CN)_6^{4-}$. The thicker film effectively insulates $Fe(CN)_6^{4-}$ from the carbon surface.

**4. NADH Oxidation on Electrode I.** It is now well known that NADH oxidizes at electrodes with a large activation energy and that this slow reaction can be accelerated by *o*-hydroquinone/quinone redox couples.[11,12] Since electrodes formed by coating **7** on carbon electrodes were effective in this regard, it was expected that I would also be useful.

An example of the catalysis of NADH oxidation achieved by I ($\Gamma_i = 7.5 \times 10^{-10}$ mol cm$^{-2}$), at pH 7 and $\nu = 50$ mV/s, is shown in Figure 5. In comparison to the first sweep voltammogram ($i_{pa} = 0.7$ μA, $E_p^a = 200$ mV) in its absence, 0.5 mM NADH tremendously enhances the anodic peak current ($i_p^a = 7.3$ μA, $E_p^a = 240$ mV) and substantially depresses the cathodic peak current. The second sweep shows smaller currents. The electrode was then removed from the NADH solution, rinsed with distilled water, and immersed into the pure supporting electrolyte. The cyclic voltammogram in this pure supporting electrolyte shows the redox couple of the catechol moiety with $i_p^a = 0.6$ μA. This indicates that the catechol moieties have not been rapidly destroyed by the catalytic oxidation of NADH.

Remembering that $\Gamma_{coul}$ has a limiting value of about $3 \times 10^{-9}$ mol cm$^{-2}$, it is of interest to measure the rate of the catalyzed NADH reaction at various values of $\Gamma_i$. To do this, $i_{CAT}$, the difference in peak current for electrode in the presence and absence of NADH, was taken as a measure of the peak current used for NADH oxidation. As shown in Figure 6, $i_{CAT}$ increases to a maximum when $\Gamma_i = 8.0 \times 10^{-10}$ mol cm$^{-2}$. It was previously shown that this $\Gamma_i$ value gave $\Gamma_{coul} = 2.0 \times 10^{-10}$ mol cm$^{-2}$. Thus,

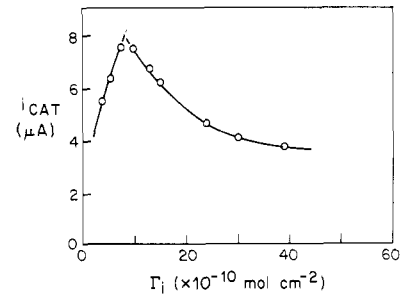



**Figure 6.** Catalytic current from $4.3 \times 10^{-4}$ M NADH is 0.05 M, pH 7 buffer on electrode I, 50 mV s$^{-1}$, as $\Gamma_i$ changes.

**Table V.** Voltammetric Data for Electrode I with NADH[a]

| $\nu$ (mV s$^{-1}$) | $i_T$[b] (μA) | $i_{CAT}$[c] (μA) | $i_{CAT}/\nu^{1/2}$ (μA s$^{-1/2}$ mV$^{1/2}$) |
|---|---|---|---|
| 5 | 0.13 | 2.9 | 1.3 |
| 10 | 0.27 | 3.9 | 1.2 |
| 20 | 0.50 | 5.8 | 1.3 |
| 50 | 0.96 | 8.7 | 1.2 |
| 100 | 1.63 | 10.1 | 1.0 |
| 200 | 2.79 | 12.6 | 0.9 |
| 500 | 5.37 | 18.5 | 0.8 |

[a] $6.2 \times 10^{-4}$ M NADH in 0.5 M pH 7 buffer, 0.1 M KCl, $\Gamma_i = 8.2 \times 10^{-10}$ mol cm$^{-2}$. [b] Peak current at 0.25 V from electrode I in the absence of NADH. [c] See text.

at this maximum, there is approximately one monolayer of active quinone formed on the surface which can act as a catalyst. Since this maximum $i_{CAT}$ is essentially the same as $i_p^a$ for NADH on bare carbon, it demonstrates that NADH is oxidized at a rate controlled by the diffusion of NADH through the solution phase. As $\Gamma_i$ is increased beyond $1.5 \times 10^{-9}$ mol cm$^{-2}$, $\Gamma_{coul}$ increases minimally and $i_{CAT}$ decreases. This is ascribed to the fact that there are now many unoxidized hydroquinone units in the outer sublayers. These keep NADH from penetrating to the active quinone units near the surface and $i_{CAT}$ decreases. These observations and explanations correspond closely to those previously reported for NADH oxidation on electrodes modified with polymer **7**.[12]

Although theories do not exist which describe the expected quantitative dependence of $i_{CAT}$ on sweep rate, it is of interest to explore this point. The data are in Table V for electrodes with the optimal $\Gamma_i = 8.2 \times 10^{-10}$ mol cm$^{-2}$. Because the polymer is unstable at $\nu \leq 50$ mV s$^{-1}$ in the absence of NADH, no rational treatment of the data is possible. It is noted, however, that $i_{CAT}/\nu^{1/2}$ is almost constant. This makes sense if NADH oxidation is diffusion controlled as proposed above for electrodes with this $\Gamma_i$. Thus at $\nu < 0.1$ V s$^{-1}$ the rate of the hydroquinone/quinone reaction and the rate of quinone reacting with NADH are both rapid enough to ensure diffusion-controlled rates of NADH oxidation.

## Summary

Electrode I has been shown by voltammetry and HPLC to release dopamine into pH 7 solution at −0.9 V. This constitutes the first example of an electrode designed to release chemicals on call. This electrode will also give quinone units on the surface at 0.20 V. Propagation of redox reactions through the polymer layer for either the anodic or cathodic process is not fast on the time scale of tens of seconds. At 0.2 V the electrode is capable of oxidizing NADH at diffusion-controlled rates.

**Acknowledgment.** This work was supported by the National Science Foundation. Data on analogous isonicotinate reductions were supplied by M. Van Lente.

**Registry No. 1**, 86339-10-8; **2**, 10354-58-2; **3**, 86260-48-2; **4**, 9080-67-5; **5**, 82741-47-7; **6**, 82741-49-9; isonicotinic acid, 55-22-1; *n*-$C_4H_9NH_2$, 109-73-9; $C_6H_5CH_2Cl$, 100-44-7; chloromethylated styrene, 30030-25-2; 3,4-(dibenzyloxy)phenethylamine·HCl, 1699-56-5; dopamine, 51-61-6.